Current Biology, Vol. 15, R730–R738, September 6, 2005, ©2005 Elsevier Ltd. All rights reserved. DOI 10.1016/j.cub.2005.08.023

The Development of Neuronal Morphology in Insects

Review

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Neurons are highly polarized cells with some regions specified for information input — typically the dendrites — and others specialized for information output — the axons. By extending to a specific location and branching in a specific manner, the processes of neurons determine at a fundamental level how the nervous system is wired to produce behavior. Recent studies suggest that relatively small changes in neuronal morphology could conceivably contribute to striking behavioral distinctions between invertebrate species. We review recent data that begin to shed light on how neurons extend dendrites to their targets and acquire their particular branching morphologies, drawing primarily on data from genetic model organisms. We speculate about how and why the actions of these genes might facilitate the diversification of dendritic morphology.

The intricate and varied shapes taken by the dendrites and axons of different neurons are not only one of the most visually striking features of the nervous system, but determine at a fundamental level how nervous systems are wired up. Recent studies have begun to build a molecular understanding of the various stages of dendritic morphogenesis, including dendrite elongation, targeting, branching and remodeling [1–5]. Owing largely to the development of key technologies for imaging and genetic manipulation of neurons [6–8], researchers have been able to ask many basic questions that were not so long ago either impossible or prohibitively difficult: How are dendrite and axon polarity specified? How do dendrites extend to their proper targets? How do dendrites grow and branch and what is the significance of particular branching patterns? What is the role of neuronal activity in morphogenesis? What are the similarities and differences between dendritic and axonal development? Ongoing screens in *Drosophila* for genes involved in morphogenesis, and comparative studies involving other invertebrate and/or vertebrate systems, promise to provide molecular, developmental and functional insights into many of these problems [8–14]. As many excellent reviews have been published on the subject [1–5,15–26], we concentrate here on reviewing recent work or emerging model systems.

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Seeing the Light of Night — a Potential Function for a Specific Branching Pattern

The shapes of invertebrate neurons are usually highly characteristic: Morphologically homologous neurons can be identified from segment to segment, animal to animal, and between species. Such conservation suggests that branching patterns are functionally significant. However, particular branching morphologies might also be shaped by influences that are not obviously adaptive, such as developmental or physical constraints that might limit the shape or organization of neurons [27]. Thus, when considering the functional relevance of specific neuronal morphology, examples in which a specific alteration in branching morphology can be correlated with a novel function or behavior may be more significant than examples of evolutionary conservation.

The arrangement and morphology of photoreceptors in insect visual systems are generally well-adapted for bright light but poorly adapted for dim light, thereby supporting diurnal patterns of behavior. Bees, which have long been a model system for studies of visual behavior, are primarily day-active, fitting with the relative insensitivity of their apposition-type compound eyes (Figure 1A). However, a nocturnal lifestyle has emerged in some species of bees, perhaps allowing them to avoid predators or to exploit resources that are only available during the night. For example, the tropical nocturnal bee *Megalopta genalis* is active for only one hour before dawn and 20 minutes after dusk, when light intensity is very low [28].

How are the visual systems of such insects adapted for the demands of dim light? One potential mechanism to enhance sensitivity is to summate weak light signals during visual processing [29]. The unique branching patterns of first-order visual interneurons may provide a mechanism for spatial summation, and thereby support a nocturnal lifestyle. In bees, retinula cells within each ommatidial cartridge, the optical unit of the eye, extend axons that terminate within the first optic ganglion, the lamina, where they connect to first-order interneurons called L1–L4 neurons. In contrast to diurnal bees, in which the L-neuron fibers show limited lateral branching beyond their parental cartridge, the L-fibers of *M. genalis* branch out into several adjacent cartridges [30] (Figure 1B). The novel morphology of L-fibers in *M. genalis* could thus mediate spatial summation of signals from multiple ommatidia (Figure 1C). This relationship between branching morphology and nocturnal lifestyle in *M. genalis* is currently a correlation, but the hypothesis is strengthened by data on L-fiber branching in a larger number of insects. Wide lateral branching is found in nocturnal cockroaches, fireflies and hawkmoths, whereas L-fibers are restricted to parental cartridges in diurnal butterflies and dragonflies [30]. Ultimately, such comparative studies

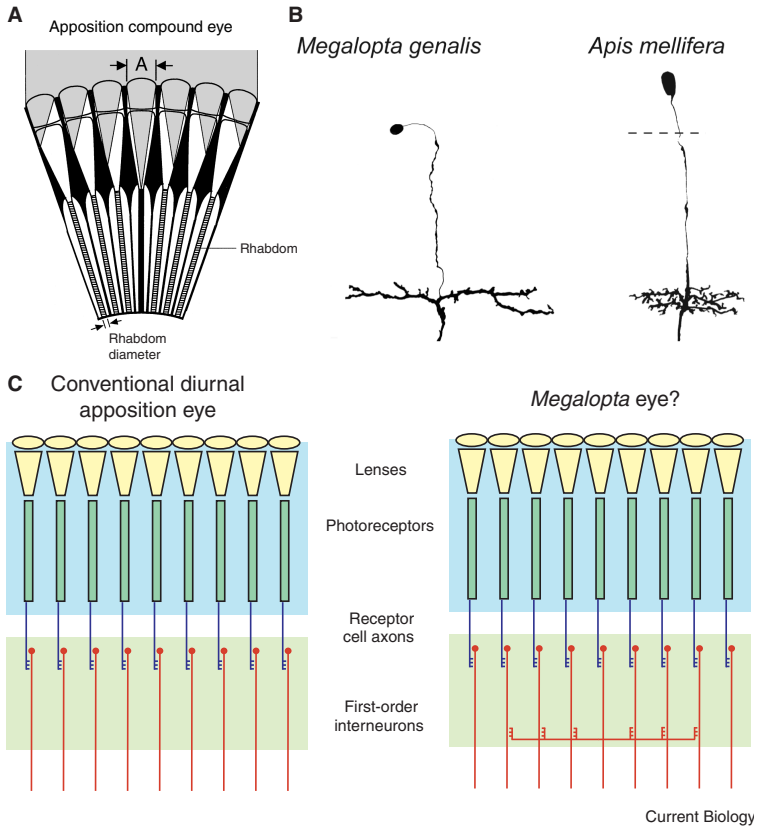

Figure 1. Neuronal morphology and nocturnal behaviour.

(A) Apposition compound eyes are characterized by a relatively narrow diameter light-collecting aperture. (B) Comparison of L-fiber lateral branching in the nocturnal *Megalopta genalis* and diurnal *Apis mellifera.* (C) Possible relevance of L-fiber lateral branching for spatial summation. In a conventional apposition eye, the processes of first-order interneurons are restricted to their parental cartridge, whereas in *M. genalis,* wide lateral branching could allow spatial summation of visual signals. Adapted from [29].

provide a unique opportunity to explore how neuronal morphology facilitates particular behaviors and lifestyles.

Dendritic Guidance: Where Do We Go from Here?

Neurons develop intricate and astoundingly diverse branching morphologies. In both vertebrate and invertebrate neurons, axons appear to emerge first from the cell body, followed by the growth of dendrites [8,31,32]. A major difference in morphology between invertebrate and vertebrate neurons is that the majority of vertebrate neurons is multipolar while the majority of invertebrate neurons is unipolar [33,34]. In a unipolar neuron, the soma gives rise to a single process, the cell body fiber, which can bifurcate into one axonal arbor and one dendritic arbor. In some cases there is no bifurcation and multiple dendritic branches form directly on the fiber [33]. By contrast in mulitipolar neurons, several processes originate from the cell body. The predominance of unipolar neurons in invertebrates and multipolar neurons in vertebrates should be seen as a quantitative, rather than qualitative, difference. Both invertebrates and vertebrates have unipolar as well as multipolar neurons and the functional specialization of dendrites and axons is observed in unipolar neurons just as in most multipolar neurons [34–37].

Following the establishment of dendrite and axon polarity, a critical next step during the process of neuronal morphogenesis is the extension of dendrites to their targets. Here, one might tend to think of axons and dendrites as distinct in their requirements. Axons extend over relatively long distances to precise targets, which suggests an *a priori* requirement for guidance mechanisms [38]. Dendrites often arborize nearer to the cell body but nevertheless show evidence of specific targeting (Figure 2) [19]. A fundamental question is whether dendrites, like axons, are guided by extracellular signals and whether similar guidance mechanisms are used by axons and dendrites. Visual examination of mature dendritic morphology is often insufficient because the same result might be accomplished by very different developmental mechanisms. For example, dendrites might be guided to their specific targets, or might grow more profusely and be selectively stabilized or eliminated in certain regions of their receptive field [39]. In *Drosophila* several classes of neurons have emerged as promising systems for identifying developmental and molecular principles that regulate dendritic targeting (Figure 2). These include motor neurons in the ventral nerve cord (VNC) [40–43], projection neurons (PNs) of the olfactory system [44–46], TTMn motor neurons of the giant fiber (GF) system [47], and the dendritic arborization (da) sensory neurons that cover the larval body wall [35,48,49].

Navigating with Extrinsic Constraints

Dendrites do not develop free from constraints imposed by surrounding cells. Substrate preferences, for example, can restrict dendritic growth or stabilization to specific two-dimensional planes, and interactions with other neurons can limit growth or provide instructions for proper targeting. One of the more dynamic examples of external constraints to dendritic growth are the

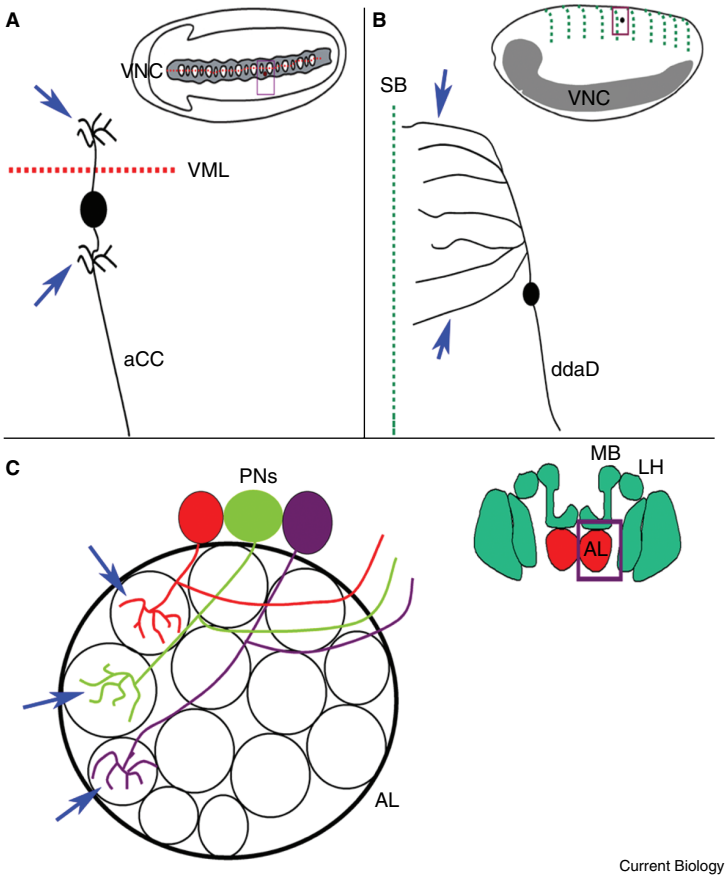

Figure 2. Dendritic guidance in the central and peripheral nervous system of *Drosophila*.

(A) Medial dendrite (top blue arrow) of an aCC motor neuron extends across the ventral midline (red; VML) during development. Removal of Netrin signals in the midline results in the failure of this dendrite to cross the midline. The upper right corner of this panel shows a schematic ventral view of a *Drosophila* embryo. The gray ladder-like structure is the ventral nerve cord (VNC), the red dotted line indicates the position of the VML, and the boxed region shows the approximate cell body position (dark circle) of aCC neuron. (B) Dendrites (blue arrows) of a class I sensory da neuron ddaD extend toward the segmental border (SB) in a near parallel fashion, suggesting that these dendrites might be guided toward the segment border during development. The identity of the guidance cues is not known. The upper right corner of this panel shows a lateral view of a *Drosophila* embryo. The boxed region shows the approximate cell body position (dark circle) of ddaD. (C) Dendrites (blue arrows) of distinct projection neurons (PNs) of the *Drosophila* olfactory system project to distinct glomeruli in the antennal lobe (AL). The PN dendrites might still use — yet to be discovered — positional cues to find their correct target. The right panel shows a schematic diagram of a dissected adult brain. The AL is boxed. MB, mushroom body; LH, lateral horn.

repulsive interactions that can take place between growing neighboring neurons [50–54]. During such interactions, neighboring dendrites will jockey for space: growing to maximize the coverage of a particular receptive area, and repelling each other to minimize the redundancy of innervation. The end result is a complete, but non-overlapping, dendritic coverage of a receptive area, an arrangement known as 'tiling' [55]. Such cell–cell interactions appear to delimit the receptive fields of sensory arbors in the leech [56,57], and the dendritic territories in the *Drosophila* peripheral nervous system [51–53,58] and vertebrate visual and somatosensory systems [50,54,59]. Ablation of a tiling neuron early in development causes biases in the direction of growth toward voided areas, suggesting that repulsion between neighboring neurons is a force that is likely to limit receptive territories [51–54].

Anatomical studies suggest that the interactions between tiling dendrites are cell-type specific [48,55,60,61]. In other words, only cells of the same morphological and functional class seem able to give or receive the 'stop' or 'turn' signal. However, the molecular mechanisms that mediate repulsive dendritic interactions have, until recently, been elusive. From a screen for genes expressed in the *Drosophila* peripheral nervous system, Furry (Fry) and Tricornered (Trc) kinase, two evolutionarily conserved regulators of the cytoskeleton, were identified and demonstrated to be involved in branching and tiling control [58]. Trc appears to normally limit dendritic branching via negative regulation of the small GTPase Rac1, a protein known to regulate dendritic morphogenesis in a variety of invertebrate and vertebrate systems [62–66]. Coimmunoprecipitation experiments indicate that Trc and Rac1 form a complex [58]. However, experiments with dominant negative and constitutively active mutant proteins indicate that Trc regulation of tiling does not depend on Rac1 and is likely to involve a distinct pathway [58]. Interestingly, both Trc and Fry are expressed not in a cell-type specific fashion, but in all da neurons, including those whose dendrites overlap significantly [58]. This suggests that Trc and Fry are either regulated differently in different types of neurons to mediate the specific repulsive signal, or cooperate with other cell-type specific tiling signals to make repulsive signaling more robust. Further studies of Trc and Fry will hopefully provide general insight into how tiling is controlled in other systems.

The molecular regulation of dendritic tiling is at least partially conserved in other invertebrates. In *C. elegans,* removal of *sax-1* and *sax-2*, homologs of *tricornered* and *furry*, respectively, causes a failure in the tiling of the mechanosensory neurons PLM and ALM [67,68]. The cellular nature of tiling by these neurons, however, is quite distinct from that of *Drosophila* da neurons. PLM development occurs in three stages: first, the PLM dendrite extends rapidly and overshoots its intended target region; second, process extension is inhibited while the animal continues to grow, resulting in a

matching of the sensory dendrite to its target; third, the animal and the dendrite grow at a similar rate, maintaining the proper coverage of the target [68]. The tiling phenotype exhibited in *sax1/2* mutant animals appears to result from a lack of growth inhibition during the second stage of the PLM development. The identity of the instructive cues for the PLM growth inhibition is not known, but it appears not to be a dendrite–dendrite repulsion mechanism, as removal of ALM does not affect the neurite termination point of PLM [68].

'Targeting' of dendrites takes on a somewhat different meaning in systems that tile via dendrite–dendrite repulsion because of the severe extrinsic constraints on dendritic growth. If tiling neurons are intrinsically capable of extending dendrites around the cell body in all directions, size and shape of the dendritic field will depend on constraints imposed by cell position, cell spacing, early growth trajectories, and rates of dendritic growth [59,69,70]. Alterations in any of these parameters during development could lead to a significant change in size or orientation of the dendritic field. For example, cell body position and the site of dendrite outgrowth can lead to an apparent bias in the trajectory of dendritic growth: the closer a neuron lies to a repulsive barrier, the more an arbor will tend towards a non-uniform (non-radial) distribution. Targeting biases are observed among certain tiling da neurons simply because these cells are not spaced as a uniform mosaic [48]. The problem of tiling demonstrates that one neuron can strongly influence the growth of nearby dendrites, and that we cannot fully understand dendritic morphology without considering the influences faced by cells in their native environments. Recent studies have made inspired efforts to elucidate extrinsic influences in olfactory and motor dendrite targeting [41,71]

Navigating with Respect to Major Landmarks

The ventral midline of *Drosophila* is a major landmark separating the bilaterally symmetric halves of the nervous system and is a source of critical guidance molecules, such as Slit, a midline repellent [72] or Netrins, mediators of midline attraction [73]. Do dendrites employ similar strategies for navigating with respect to the midline? Dendrites of the motor neurons aCC, RP3 and RP2 display a very stereotypical projection pattern with respect to the ventral midline: they either cross, as in the case of aCC (Figure 2A), or do not cross the midline, as in the case of RP2 [43]. The dendrites of aCC, however, fail to cross the midline in the absence of Frazzled [74], a receptor for Netrins, while removing Robo, the receptor for Slit [75,76], causes the RP2 dendrite to aberrantly cross the midline [43]. These results suggest that certain dendrites are indeed influenced by axon guidance molecules. This idea is further strengthened by work on the giant fiber system, a well-defined circuitry for escape behavior in *Drosophila* [47]. In the giant fiber system, the medial dendrite of the postsynaptic TTMn motor neuron extends toward, but does not cross, the ventral midline. This neuron forms a synapse with the descending giant fiber axon that is strictly ipsilateral. When Robo is overexpressed in the TTMn neurons, dendrites fail to extend to their wild-type position, resulting in stunted morphology and weakened synapse formation [47].

A unique relationship between dendrite and axon targeting was uncovered following a systematic characterization of dendritic morphology of *Drosophila* motor neurons [41]. Motor neurons that innervate the musculature of the body wall organize their dendritic territories in stereotypical positions along the anterior–posterior axis in the ventral nerve cord. Strikingly, the dendritic territories of these motorneurons are organized into domains that form a myotopic map, that is, they centrally represent the distribution of peripheral muscles (Figure 3) [41]. Furthermore, the dendritic fields of many cells occupy different domains and do not overlap with each other [41,42], reminiscent of the tiling observed with sensory dendrites (Figure 3). How are these dendritic patterns established during development? Partitioning of dendrites occurs independently of muscle innervation. Likewise, glial cells appear to play no essential role in spatial patterning as ablation of glia in the CNS does not disrupt the position of motor neuron dendritic fields [41]. Partitioning of fields by dendrite–dendrite interactions, and passive packing of fields according to cell body position or axon trajectory, also seem not to operate among at least a subset of the neurons. Instead, the organization of the myotopic map is likely set down early in embryonic development as the body is divided into parasegmental units [41].

Together, these findings raise several questions that remain to be addressed experimentally. Given the similar abilities of dendrites and axons to respond to the same guidance cues, how do they manage to project to distinct locations? For example, the axon of aCC does not cross the midline while its dendrite does. Differential localization of molecules that either confer or strip the ability of a neurite to respond to guidance cues might provide one answer. Indeed, in cultured mammalian cortical pyramidal neurons, differential localization of soluble guanylyl cyclase allows axons to be repelled but dendrites to be attracted to Sema3A [77]. Differential localization of effector molecules in a temporally distinct fashion might be another possibilty for endowing guidance specificity, as axons and dendrites often grow out at different times during development, axons typically earlier than dendrites.

In addition, certain da neurons of the *Drosophila* peripheral nervous system also appear to be guided toward or away from major body landmarks [48,49]. The primary dendrite of these neurons extends from the cell body toward the dorsal midline while the secondary branches extend toward the segmental boundaries, and do so in a direction nearly orthogonal to that of the primary branch (Figure 2B) [48,49]. Such directed dendrite projection patterns suggest the presence of guidance molecules that are perhaps either localized at the dorsal or ventral midline, at the segmental boundaries, or graded along the anterior–posterior or dorsal–ventral axis in surrounding tissues. The nearly invariant projection pattern of these neurons makes them well-suited for identification of such molecules. Indeed, several mutants

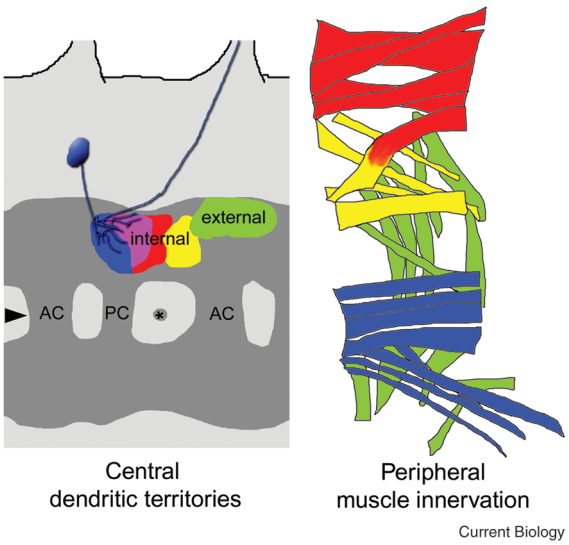

Figure 3. A myotopic map of motoneuron dendrites in *Drosophila*.

Superimposed representative *Drosophila* motor neurons of 15 hr old embryos (left panel) that innervate the muscles of the abdominal half-segment (right panel). Cell bodies reside in the cortex just outside of the neuropil (black). Fibers project from the cell body to the neuropil, where dendrites arborize, and then out of the CNS to innervate muscles. Landmarks for the segment border are indicated by asterisks. Note the parasegmental organization of the myotopic map. Color code: blue, ventral internal; yellow, dorsolateral internal; red, dorsal internal; green, external; black, neuropil; gray, cortex. Symbols and abbreviations: triangles, ventral midline; asterisks, dorsal ventral channels (landmarks for the segment border); AC, anterior commissure; PC, posterior commissure. Figure modified from [41].

uncovered from dendrite morphology screens exhibit dendrite misrouting phenotypes [8] (M. Kim, W.G, B.Y., J. Parrish, unpublished results). Detailed time-lapse analysis and identification of the genes responsible for these phenotypes should provide a basis for understanding the targeting of other neurons that share similar dendritic projection patterns.

Navigating without Obvious Landmarks

Which mechanisms will dendrites employ when they face a far more challenging task, such as deciding which specific territory to occupy within a grossly homogeneous target region? Insights into this problem have emerged from a series of studies on projection neuron (PN) dendrite targeting [44,71,78]. The PNs are second-order neurons in the fly olfactory circuit and relay sensory input received from olfactory receptor neurons (ORNs) to higher brain centers. Most PNs project their dendrites into only one of ~50 glomeruli in the antennal lobe [44]. The targeting of PN dendrites is highly stereotypical and is determined by the birth order of the PNs [44]. Recent studies indicate that in *Drosophila*, the targeting of PN dendrites is independent of inputs from the pre-synaptic ORNs, as invasion of ORN axons into the antennal lobe occurs after PN dendrite target selection [71]. The relative arrival times of axons and dendrites in the fly olfactory system appear to contrast with the results of earlier studies in *Drosophila* [79] and other insects, such as *Manduca*, in which the ORN axons, rather than the PNs, seem to be the first to accumulate into protoglomeruli and thus appear to play the primary role in glomerular development [80,81]. This contradiction may either reflect an inherent difference in wiring principles between the two species, or alternatively, may be resolved by simply separating the processes of spatial patterning of dendrites — a much earlier developmental event — from glomerular formation [71].

How is the stereotypical targeting of *Drosophila* PN dendrites accomplished in the absence of cues derived from pre-synaptic partners? One answer appears to be: intrinsic transcriptional control. Combinatorial control by transcription factors is one way by which a limited number of genes can specify several different developmental outcomes. For example, the binary on–off expression of six hypothetical transcription factors, each of which regulates one critical surface recognition molecule, can specify 64 (2^6) different kinds of surface properties. Interestingly, two transcription factors, Acj6 and Drifter, are expressed in two non-overlapping sets of projection neurons, adPNs and lPNs, that have different characteristic dendritic targets [82]. Removal of *acj6* causes a subset of the adPNs to project dendrites to incorrect targets, while ectopic expression of acj6 in lPNs causes some of the lPNs to target into adPN target areas [82]. Similar, but less dramatic, results were obtained with manipulations of *drifter*. Although specific expression of Acj6 and Drifter alone cannot explain how individual groups of PNs select their targets, differential expression of transcription factors within each set of PNs (Acj6-positive and Drifter-positive) might be an important contributor to the dendritic targeting of individual neurons.

The targeting specificity of PNs appears to involve both intrinsic transcriptional control, and interactions between dendrites. More specifically, homotypic attractive interactions among dendrites of the same PN class or heterotypic repulsive interactions of dendrites of distinct classes might contribute to targeting specificity via a sorting mechanism [71]. Experimental support for this concept comes from data showing that projection neurons lacking N-cadherin, a homophilic adhesion molecule, project dendrites to the correct glomeruli, but these dendrites often ‘spill-over’ into adjacent glomeruli [83]. Furthermore, the spill-over effect is observed even when the projection neuron examined is wild-type for N-cadherin but is surrounded by neurons that are mutant [83]. This result raises the possibility that N-cadherin dependent homotypic interactions among projection neurons that aim for the same target might act to ‘glue’ the dendrites of PNs together, thereby achieving highly specific targeting.

How Do Neurons Grow and Branch? An Adult Perspective

In both vertebrate and invertebrate neurons, the elaboration of dendritic branches is a highly dynamic process [8,53,84–88]. Because very many of the branches formed on developing neurons do not persist, the course of morphogenesis cannot be

reconstructed simply by examining mature neuron morphology [86]. Fundamental to our understanding of the mechanisms of dendrite branching are time-lapse imaging studies in live preparations. However, for many neurons, *in vivo* imaging of arbors is limited by the availability of suitably specific and robust markers of early growth and elaboration. A special feature of many insect neurons, namely, their ability to prune and re-grow most of their arbors during metamorphosis to the adult stage [9,25,89–92], has allowed detailed *in vivo* time-lapse studies of morphogenesis.

A particularly advantageous system for *in vivo* imaging during metamorphosis is the da sensory system of *Drosophila*. First, da neurons lie immediately beneath the transparent cuticle and branch in only two dimensions [35], making it relatively straightforward to image entire arbors during development. Second, fluorescent markers can be used to label different groups of these neurons and follow their growth *in vivo* [8,51–53,58,93]. Finally, several of the da neurons survive metamorphosis to prune and re-grow their dendritic arbor [87,93–95]. As the arbors re-grow, the animal is stationary and dendritic elaboration occurring just beneath the cuticle is amenable to quantitative *in vivo* time-lapse studies.

For instance, one da neuron (ddaE) develops a simple morphology in embryonic stages, deconstructs its arbor during early metamorphosis by both local degeneration and branch retraction and grows a much more complex adult-specific arbor [48,49,53,87,93]. Multiphoton imaging of intact pupae revealed that adult dendritic growth of ddaE occurs in two distinct phases: scaffold building and filling in of the receptive territory by fine branches [87]. During the first stage, many short filopodia extend and retract from the small primary dendrites and some stabilize to serve as a scaffold for the mature arbor. This dynamic growth phase resembles the dynamic branching observed in pyramidal neurons in slice culture and the rapid *in vivo* growth of optic tectal neurons in *Xenopus* [84,85]. In the second stage of ddaE's adult growth, the dendritic scaffold remains stable and fine branches elaborate to fill in the dendritic territory [87]. Branch retraction programs dominate the first phase of arbor development, but are largely absent from the second phase [87]. The transition between these phases is controlled by juvenile hormone — a developmental hormone that along with ecdysone coordinates insect development. Application of a juvenile hormone mimic during the first phase of adult-specific morphogenesis, when juvenile hormone is normally absent, leads to a decrease in mature arbor complexity by maintaining retraction programs into late stages of morphogenesis [87].

The above data suggest that early dynamic extension and retraction of arbors, common to both vertebrates and invertebrates, allow dendrites to assume a basic shape, or scaffold [84,85,87,96]. Switching off retraction programs may subsequently allow a neuron to achieve an appropriate complexity [25]. Thus, the regulation of dendritic stability during development seems to have a central role in morphogenesis and in morphological diversification. It seems likely that the onset or progress of the 'filling in' phase of morphogenesis could be modulated differently in different types of neurons to produce divergent degrees of branch complexity.

Specifying Dendrite Branching Pattern

With their diverse yet stereotyped morphologies, invertebrate neurons are ideally suited to address the fundamental problem of how a neuron achieves a cell-specific or class-specific branching pattern. The ability to identify individual neurons by physiological and morphological criteria suggests that genetic mechanisms control many aspects of neuronal morphology [97].

Various strategies have been used to explore the genetic basis of branching morphology in insects. Among the most successful have been forward genetic screens and studies of candidate genes in *Drosophila*. The predominant assays are loss-of-function and gain-of-function analysis, often performed using mosaic approaches to separate cell autonomous from non-autonomous genetic control [7]. The genes identified by such approaches can be roughly categorized into those that seem relatively selective in their control of dendritic morphology, and those that exhibit broad control over many aspects of morphology, such as targeting, branch number, branch length. Examples might include those that regulate terminal branch number or branch length, such as Rho family GTPases [58,65,98], the serine/threonine kinase Tricornered [58] and the RNA binding proteins Nanos, Pumilio [99] and Fmr1 [65]. Modification of the activity of these genes often causes neurons to develop arbors having either more or fewer branches, or significantly different branch lengths. Because they control specific aspects of morphogenesis, manipulation of these genes causes neurons to adopt morphologies that are normally not observed *in vivo*. Examples of genes that coordinately control several class-specific aspects of neuronal morphology have emerged from several recent studies in *Drosophila* [82,100–103] and in each case these encode putative transcription factors, including zinc finger, homeodomain, POU-domain, and BTB domain containing proteins. Loss- or gain-of-function manipulations of these genes cause cells to adopt branching morphologies that are quantitatively or qualitatively more like those of distinct neurons or neuronal classes, implying that morphological identity is under transcriptional control in many — if not all — types of neuron.

These findings raise the general question of whether morphological identity is genetically separable from cell fate. One way of approaching this problem is to examine the expression of multiple markers of cell identity in mutant neurons. However, often the marker genes have not been ascribed a function and thus cannot be excluded from being regulators of morphogenesis themselves. This can in some cases present a conundrum when manipulating the activity of transcription factors, which are expected to act by altering gene expression. Alternatively, we can ask: When during development is morphological identity specified and how specifically is a

particular gene regulating morphology? At one extreme, genes that endow neuronal precursors with their identity might supply progeny neurons with their 'branching program'. At the other extreme, cell-type specific morphology might require continuous action of dedicated transcriptional regulators in post-mitotic neurons. These alternatives might be addressed at a very basic level by examining the temporal expression patterns of genes of interest and by examining the morphological consequences of manipulating levels of gene activity at different stages.

Returning to the transcription factors mentioned above, the zinc finger transcription factor Hamlet is expressed around neuronal birth [100]. The POU-domain protein Drifter and the homeodomain protein Cut are expressed both in neuronal precursors and in differentiated neurons [82,101], while the POU-domain protein Acj6 and the BTB Zinc finger protein Abrupt are expressed predominantly or exclusively in post-mitotic cells [82,102,103]. Together with the finding that dendrite morphology can be altered by post-mitotic overexpression of any of these genes, these data suggest that neuronal morphology can be controlled at the level of transcription both in neuronal precursors and in post-mitotic neurons.

Our understanding of what causes different types of neuron to take reliably distinct branching patterns is clearly incomplete. The above results indicate that a key future goal is to identify transcriptional regulators and their targets that control morphogenesis. First steps have been taken with the zinc-finger transcription factor Sequoia: microarray experiments indicate that it regulates genes involved in neurite morphogenesis rather than genes controlling cell fate [104]. In many cases, however, these genes are expressed in morphologically heterogeneous populations of neurons, and even non-neuronal cells, thus it would be informative to profile restricted groups of neurons [105–107]. A concurrent goal will be to understand how these and other regulators act on the different phases of dendritic growth; for example, scaffold building and territory filling in the case of adult — and perhaps also embryonic — sensory neurons. As genes that emerge from such screens are examined in greater depth, we may hope to converge on core conserved signaling programs that regulate dendritic morphogenesis.

The 'Why' of Dendritic Morphological Diversity

One consistent feature of dendritic morphology is its diversity across cell types and species. Why have different neurons attained such extraordinarily diverse shapes? It has been proposed that change during metazoan evolution is constrained by both developmental complexity and the prior attainment of a certain degree of developmental stability [108]. As the number of interacting elements (i.e., complexity) increases, it becomes increasingly rare for any mutation to improve the interactions between elements without harming them. Above all, any system — in particular the nervous system — must remain functionally coherent in the face of evolutionary change [108]. Once coherence is achieved, it is further reinforced, because subsequent changes are screened for their compatibility with the existing organization [108]. It is important, then, to identify which features of neurons are most able to change without paralyzing the network. The basic compartments for information input and output, as well as the mechanisms for intracellular and intercellular information propagation are well-conserved. It might be that alterations in dendrite morphology are one way of tinkering with the functionality of the nervous system during evolution with little risk of failure. The ultimate consequence of so many successful — or at least not unsuccessful — random experiments by nature is the extraordinary diversity of morphology that we observe.

Acknowledgments

Our work is supported by the NIH and Jane Coffin Childs Foundation. Y.N.J. is an Investigator of the Howard Hughes Medical Institute.

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